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ON
August 16, 2004
DATE

Thomas R. Papale
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Attorney Docket No.: B45226

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Friede et al.	June 24, 2004
Appln. No.:	10/088,748	Group Art Unit: 1648
Filed:	July 19, 2002	Examiner: Z. Lucas

For: INTRANASAL INFLUENZA VIRUS VACCINE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. CHRISTIAN VAN HOECKE

I, Dr. Christian Van Hoecke, a citizen of Belgium and residing at rue du Jardinage, 44, B-1082 Brussels, Belgium, declare the following:

1. I received a Medicine Degree in 1971 with First Class Honours from the Free University of Brussels, Belgium. I joined SmithKline Beecham Biologicals (the predecessor of GSK Biologicals) in 1989. I am currently an employee of GSK Biologicals where I am Director Clinical Development and responsible for the development of several vaccines, including the Influenza virus vaccine.

2. I have read and am familiar with United States Patent Application No. 10/088,748, and have carefully reviewed the Office Action mailed on March 25, 2004.

3. As set forth in Example 4 of the patent application, the Applicants have established the immunogenicity of a one-dose intranasal split influenza vaccine in healthy human adult subjects. The intranasal split trivalent influenza formulation tested in that example contained 30 μg HA per strain and a combination of Triton X-100 and Tween 80 surfactants. Data obtained from intranasal administration of this formulation was compared to data obtained from parenteral administration of a licensed, conventional, influenza vaccine (Fluarix™).

4. Example 5 describes experiments conducted in the same target population with a trivalent split influenza vaccine adjuvanted with another surfactant, Laureth-9. Immunogenicity results were comparable to those obtained after parenteral administration of the conventional Fluarix™ vaccine. Moreover, the intranasal formulation generally produced a better mucosal IgA response after one dose than did the parenteral vaccine.

5. Example 7 of United States Patent Application No. 10/088,748 set forth another experiment, in human healthy adults, wherein low doses of influenza vaccine are administered and compared with results achieved with parenteral administration of the conventional Fluarix™ vaccine. A summary of the results of the clinical trial described in Example 7 are presented below.

6. Table 6, found at page 45 of the '748 application, is reproduced below with two additional columns inserted. The experimental group number in presented in order to facilitate interpretation of the data presented in the table in paragraph 7 supra. In addition, the right-most column indicates whether the outcome of this trial achieved at least one of the European Union official criteria for an effective vaccine against influenza.

Table 6 : General description of the vaccines

Administration	*Antigen per dose (µg HA/strain)*	*Additional Reagent?*	*Group*	At least 1 criterium for each strain
intranasal	30 µg	No	(group 3)	yes
intranasal	15 µg	No	(group 2)	yes
intranasal	15 µg	Laureth-9	(group 1)	yes
intranasal	7.5 µg	Laureth-9	(group 6)	yes
intranasal	7.5 µg	Laureth-9 + 3D- MPL	(group 4)	yes
intramuscular	15 µg	No	(group 5)	Yes (control)

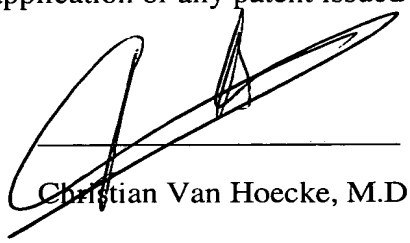
7. More detailed results of the clinical trial are presented in the Table below:

IMMUNOGENICITY RESULTS: The immunogenicity results were as follows:						
Group	**1**	**2**	**3**	**4**	**5**	**6**
Conversion factor	**European Standard: >2.5**					
A/ NEW-CALEDONIA	4.2	3.8	5.3	2.6	34.3	3.1
A/SYDNEY	2.5	2.6	3.2	1.8	7.1	2.7
B/YAMANASHI	3.9	2.2	3.3	2.5	13.2	1.5
Seroconversion rate	**European Standard: >40%**					
A/ NEW-CALEDONIA	55.0	45.0	57.9	30.0	95.0	45.0
A/SYDNEY	35.0	30.0	31.6	20.0	70.0	35.0
B/YAMANASHI	50.0	20.0	47.4	40.0	80.0	15.0
Protection rate	**European Standard: >70%**					
A/ NEW-CALEDONIA	95.0	100.0	100.0	90.0	100.0	80.0
A/SYDNEY	100.0	90.0	100.0	95.0	100.0	90.0
B/YAMANASHI	95.0	95.0	94.7	95.0	100.0	90.0

8. These data demonstrate that for all intranasal, single dose vaccines tested (i.e., groups 1-4 and 6), at least one of the European Union official criteria (protection rate) are met for all strains of influenza virus tested. It should be noted that even the lowest dose of haemagglutinin (7.5 ug per strain) without immunostimulant (group 6), the criteria were met.

9. The Applicants have therefore successfully demonstrated a method to achieve significant prophylaxis against influenza infection or disease by administration of a single dose of a composition comprising a split influenza virus antigen preparation. Moreover, prophylaxis was achieved at several doses of haemagglutinin, including doses as low as 7.5 µg per strain.

10. I declare that all statements made herein based on my own knowledge are true and that all statements based on information and belief are believed to be true; and further that the statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above application or any patent issued therefrom.



Christian Van Hoecke, M.D.

Date: 29 / 07 2004

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